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Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

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(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Stable topiramate formulations

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Stable Topiramate Formulations

Field of the invention

This invention relates to bi- or multiphasic tablets containing an active ingredient that is moisture sensitive and at least one layer that comprises hygroscopic matrix material and to processes for manufacturing such tablets.

Background of the Invention

Typical formulations that are used for oral administration of pharmaceutically active

4,513,006 and 5,387,700 and, preferably, by the process described in Examples 1 to 3 of U.S. Patent No. 5,387,700.

Exposure to moisture and heat, though, causes the topiramate active agent in the solid dosage form to degrade. Topiramate in particular is very sensitive to water (humidity). Upon contact with humidity, topiramate degrades quickly and degradation accelerates because the degradation products have a catalytic effect on the degradation process itself. Degradation of topiramate tablets is readily detected by changes in physical appearance (discoloration of tablet color to brown or black) and by the formation of sulfate ions and organic degradation compounds, which can be readily detected by standard techniques known to those of ordinary skill in the art. Topiramate should therefore be well protected from moisture.

To further improve tablet quality and to prevent degradation of topiramate active ingredient, tablets are dried intensively to lower the amount of water in the tablets as much as possible to prevent the degradation of topiramate. Another reason for intensively drying the tablets is the so-called "greenhouse effect". Any small amount of water that is present in topiramate tablets and/or that is locked into the cavities of a blister packaging negatively influences the stability of topiramate.

To maintain tablet quality, topiramate tablets have been packaged into both high-density polyethylene (HDPE) bottles containing a desiccant and blister packages containing a desiccant. Stability testing over time has demonstrated that the tablets in such packages have been preserved under various temperature, humidity and light conditions. Blister packages, however, offer advantages over the HDPE bottles used in the current marketed package and are, therefore, a preferred packaging format for topiramate tablets. Blister packages match the stability and marketing characteristics of HDPE bottles while being less expensive to package, lighter in weight and more conveniently stored; in addition, they offer rapid access, unit dose accountability and better physical protection for the product. Blister packages are especially advantageous for packaging moisture sensitive tablets such as topiramate because each tablet cavity

then becomes a primary container in direct contact with the tablet, inherently enclosing a minimum of air and associated moisture.

Tablet stability in a blister package, therefore, becomes a function of the physical characteristics of the materials used in the composite blister package which affect permeability to moisture vapor and the ability to protect the enclosed product from light and humidity. Although other factors affect tablet stability, such as tablet moisture content and the packaging environment itself, manufacturers and packagers have focused on enhancing the stability and performance of blister packages by providing cavities for additional materials such as desiccants in addition to the tablet cavities.

WO 01/89445 describes a blister package for topiramate tablets which preserves stability of the active ingredient without a desiccant contained therein. This blister package comprises a pan sheet having preformed cavities containing pre-dried topiramate tablets and a cover sheet sealed to the pan sheet.

Currently marketed topiramate tablets are packaged in particular blister packages such as described in WO 01/89445. These packages are relatively expensive and the need for careful drying step of the topiramate tablets prior to packing is cumbersome.

There is a need for topiramate tablets that are stable in themselves and that do not need the pre-drying step or need limited pre-drying and further can be packed into standard blister packages. These needs are met by the bi- or multiphasic tablets in accordance with the invention.

Summary of the invention

The present invention is concerned with bi- or multiphasic tablets comprising an effective amount of topiramate, wherein at least one of the phases comprises hygroscopic matrix material and wherein none of the phases contains both topiramate and hygroscopic matrix material.

In particular embodiments, the invention concerns a biphasic tablet having a phase that comprises an effective amount of topiramate and another phase that comprises hygroscopic matrix material.

In certain embodiments, the invention is concerned with bi- or multilayered tablets comprising an effective amount of topiramate, wherein at least one of the layers comprises hygroscopic matrix material and wherein none of the phases contains as well topiramate and hygroscopic matrix material.

In particular embodiments, the invention concerns a bilayered tablet having a layer that comprises an effective amount of topiramate and another layer that comprises hygroscopic matrix material.

In further particular embodiments, the hygroscopic matrix material is a hygroscopic polysaccharide, in particular a gum, more in particular alginate, gum Arabic or xanthan gum, the latter being preferred.

In a further aspect, there is provided a bi- or multiphasic tablet topiramate, wherein at least one of the phases essentially consists of hygroscopic matrix material and wherein none of the phases contains both topiramate and hygroscopic matrix material.

In a further aspect, there is provided a bi- or multilayered tablet comprising an effective amount of topiramate, wherein at least one of the layers essentially consists of hygroscopic matrix material and wherein none of the layers contains as well topiramate and hygroscopic matrix material.

In a further aspect there is provided a process for manufacturing a bi- or multiphasic tablet in accordance with the invention, comprising compressing two or more pre-shaped phases in an appropriate compressing apparatus.

In a further aspect there is provided a process for manufacturing a bi- or multilayered tablet in accordance with the invention comprising compressing a suitable topiramate

containing composition as to form a layer, laying hygroscopic matrix material on this topiramate containing layer, compressing the whole, and if desired laying further compositions of topiramate and/or further hygroscopic matrix material thereon and each time subjecting the whole to a compression and if further desired coating the thus prepared dosage form.

In a further aspect there is provided a process for manufacturing a bi- or multilayered tablet in accordance with the invention comprising compressing hygroscopic matrix material composition as to form a layer, laying a suitable topiramate containing mixture on this hygroscopic matrix material containing layer, compressing the whole, and if desired laying further compositions of topiramate and/or further hygroscopic matrix material thereon and each time subjecting the whole to a compression and if further desired coating the thus prepared dosage form.

Topiramate tablets having a phase that contains hygroscopic matrix material are more stable in that the degradation of topiramate is prevented.

In a further aspect, there is provided a bi- or multiphasic tablet according to the invention containing an effective amount of topiramate having at least one phase or layer that contains from about 20 % to about 100 %, in particular from about 30 % to about 90 % or from about 50 % to 80 % of hygroscopic matrix material.

In a particular embodiment the tablets according to the present invention are coated with an appropriate coating. The coating may be for taste masking or other purposes.

Furthermore, the invention concerns a method of treating a warm blooded animal suffering from analgesia, said method comprising the administration of an oral dosage form containing an effective amount of topiramate, said dosage form being as described

Detailed description of the invention

The tablets of the invention contain topiramate which is a moisture sensitive active ingredient. The tablets of the invention further contain a hygroscopic matrix material which is any material that is able to form a matrix and which is capable of attracting water. Particular hygroscopic matrix materials are those mentioned above.
As used herein, 'alginate' refers to alginate or its salts, in particular to its alkali metal salts such as sodium or potassium salts.

The tablets according to the invention contain at least two phases. As used herein the term 'phase' refers to a defined three dimensionally shaped section in a tablet dosage form that contains the same material and wherein each phase is separated from the other. Examples of phases are layers, which are incorporated in bi- or multi-layered tablets. Other examples are cylindrical, spherical or other tridimensionally shaped sections that can be present in tablets. This gives rise to different tablet formats such as the so-called 'bull-eye' tablets, or concentric tablets (a central cylindrically shaped section surrounded with one or more further cylindrical layers (i.e. a ring-like combination), or 'coated' tablets wherein the coating is a layer completely surrounding a tablet nucleus and the like tablet formats. Preference is given to bi- or multi-layered tablets.

Preferably a phase comprising hygroscopic matrix material is adjacent to a phase containing topiramate.

The tablets of the invention may be biphasic, which is preferred, or multiphasic, i.e. having 3,4, 5 or more layers. At least one layer should comprise hygroscopic matrix material but in case of multiphasic tablets, more than one layer comprising hygroscopic matrix material can be present.

Particular embodiments are tablets that contain topiramate which may be present in amounts from about 10 mg to 500 mg topiramate per unit, preferably from about 25 mg

compressed or suitable topiramate mixtures can be employed for direct compression, e.g. starting from a suitable powdery mixture. Subsequently the hygroscopic matrix material is contacted with the compressed topiramate phase as to form another phase and the whole is compressed. In case of bi- or multilayered tablets the hygroscopic matrix material is laid onto the topiramate tablet so as to form a layer and the whole is compressed to a biphasic tablet.

In a particular aspect the invention concerns a process for manufacturing a tablet as described herein, comprising direct compression of a mixture of an effective amount of topiramate with suitable ingredients as to form a layer and laying hygroscopic matrix material on this layer and compressing the whole. In case of direct compression the other ingredients preferably are a suitable filler and a suitable lubricant. The mixtures for direct compression preferably contain a lubricant, in particular magnesium stearate. They may additionally contain a filler, in particular a sugar such as lactose. They may furthermore contain a flow enhancer such as colloidal silica (silicon dioxide). In the mixtures for direct compression the lubricant preferably is present in concentrations in the range of about 0.75 % to about 1.0 %. The filler is present in concentrations from about 5 % to about 80 %, preferably from about 10 % to about 65 %, more preferably from about 20 % to about 50 %. The flow enhancer is present in concentrations from about 0.4 % to about 0.6 %, preferably about 0.45 % to about 0.50 %. All percentages herein are w/w relative to the total weight of the dosage form.

Preferred embodiments of the invention are tablets and more preferably these are coated, in particular film-coated. Coated tablets are easier to swallow than uncoated tablet cores, are usually easier to distinguish from other tablets - in particular when the film-coat contains a dye or a pigment -, and may furthermore have an improved stability (shelf-life). Coating can be done for taste masking purposes because of the bitter taste of topiramate. Coatings are applied using conventional methods using art known materials usually applied for this purpose. Particularly attractive coating products are based on suitable film-forming polymers such as hydroxypropylmethylcellulose (HPMC) or polyvinylalcohol (PVA). Preferably, a

plasticizer is added. Examples of suitable plasticizers are polyethylene glycol or derivatives thereof such as polyethoxylated alkylglycerides, e.g. polyethoxylated stearyl monoglyceride, in particular the material sold under the trade name Macrogol™. Further ingredients may be added to the coating such as fillers, dyes or pigments, flavors, sweeteners and the like components. Examples of such further ingredients are lactose, titanium dioxide, starch and the like.

Particularly suited as coating materials for the dosage forms of the invention are the Opadry™ materials, which mainly contain the before mentioned materials and further ingredients such as plasticizers, e.g. polyethylene glycol.

The tablets in accordance to the invention can be packaged in standard blister packages without intensive pre-drying, or where appropriate, with limited pre-drying. This makes the present tablets easier to handle and to package. The tablets in accordance with the present invention are easy to produce and are cost-effective because more simple and cheaper packaging techniques can be used and also the cumbersome drying step of the tablets prior to packaging can be avoided.

Moreover, the presence of a phase containing hygroscopic matrix material has a positive effect on the stability of topiramate. Without being bound by theory, this can be explained by the fact that the hygroscopic matrix material absorbs the water away from the topiramate containing phases of the tablet.

Examples

Formulation example 1:

Hygroscopic matrix material layer:

Active and Excipients	mg/Tablet
Tramadol HCl	10.00
Xanthan Gum	120.00
Lactose	165.65
Magnesium Stearate	3.00
Silicon Dioxide	1.35
Total	300.00

Topiramate (moisture sensitive) layer:

Active and Excipients	mg/Tablet
Topiramate	16.00
Lactose Monohydrate	19.744
Pregelatinized Starch	4.096
Microcrystalline Cellulose	8.8
Sodium Starch Glycolate	2.56
Magnesium Stearate	0.256
Total	51.456

Formulation example 2:

Hygroscopic matrix material layer:

Active and Excipients	mg/Tablet
Tramadol HCl	100.00
Xanthan Gum	300.00
Lactose	43.25

Magnesium Stearate	4.50
Silicon Dioxide	2.25
Total	450.00

Topiramate (moisture sensitive) layer:

Active and Excipients	mg/Tablet
Topiramate	128.00
Lactose Monohydrate	157.952
Pregelatinized Starch	32.768
Microcrystalline Cellulose	70.4
Sodium Starch Glycolate	20.48
Magnesium Stearate	2.048
Total	411.648

Claims

1. A bi - or multiphase tablet containing a moisture sensitive active ingredient and at least one layer that comprise hygroscopic matrix material.

2. A bi - or multiphase tablet containing a moisture sensitive active ingredient. The said active ingredient is preferably topiramate or salt thereof.

3. A dosage form according to claims 1 or 2 wherein the dosage form contains topiramate in various strengths from about 10 mg to 500 mg per unit.

4. A dosage form according to any of claims 1 – 3 wherein the hygroscopic matrix material is alginate or salt thereof or xanthan gum.

5. A dosage form according to any of claims 1 – 4 wherein the hygroscopic matrix material is preferably xanthan gum.

6. A dosage form according to any of claims 1 – 5 wherein the formulation protects the moisture active ingredient from the greenhouse effect.

7. A dosage form according to claims 1 - 6 containing at least one phase or layer that contains from about 20 % to about 100%, in particular from about 30% to about 90% or from about 50% to 80% of hygroscopic matrix material.

8. A dosage form according to any of claims 1 – 7 wherein the dosage form is coated with a taste masking coating.

9. A dosage form according to any of claims 1 – 8 wherein said dosage form is coated with a suitable film-forming polymers such as HPMC or PVA, preferably with a plasticizer.

10. A dosage form according to any of claims 1 - 9 wherein the oral pharmaceutical dosage form of the invention comprises defined unit doses.

Abstract

Stable Topiramate Formulations

This invention relates to bi- or multiphasic tablets containing an active ingredient that is moisture sensitive and at least one layer that comprises hygroscopic matrix material and to processes for manufacturing such tablets.